Pituitary (2006) 9:163–164
DOI 10.1007/s11102-006-0389-4

Guest editorial

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Published online: 10 October 2006

It is a great honor and pleasure for me to serve as a guest editor and organize a special issue on Neuroendocrine Tumors. All the invited authors are well established scientists known around the world. They made a tremendous contribution here by overviewing each topic precisely, including a part of their own data, to cover the topic from the fundamental knowledge to the most up-to-date advancements in the basic and clinical problems of neuroendocrine tumors.

According to the World Health Organization's definition of neuroendocrine tumors, which is morphofunctional and primarily based on microscopic characteristics including the identification of hyperfunctioning endocrine tumors [1], these neoplasms form a diverse group of conditions with a large spectrum of clinical syndromes depending on the presence of secreted hormones. Clinical management of neuroendocrine tumors is quite challenging with new diagnostic and therapeutic approaches already available or emerging, especially after the introduction of genetic screenings that have led to a significant improvement of patients' treatment and counseling. Of course despite our desire it would be impossible to comprehensively cover all the relevant issues, but all possible attempts were made to address pituitary-related tumors, familiar multiple endocrine neoplasia and some other diseases involved.

First, an advanced molecular biology analysis of neuroendocrine tumors is thoroughly summarized to overcome the limitations of microarray experiments, inspiring many new ideas about future directions of molecular studies in neuroendocrine tumorigenesis and development of novel therapeutic strategies. For instance, a deep analysis of the *RET* proto-oncogene induced changes gives us not only an understanding of the diversity of RET-dependent signal transduction mechanisms but also warrants a necessity of further investigation of the genotype-phenotype correlations together with the development of novel molecular targeting treatment means for multiple endocrine neoplasia. It is noteworthy that knowledge of metabolic and signaling pathways of small molecules in neuroendocrine tumor cells has already resulted in a successful implementation of therapeutic regimens in cell culture and animal models; progress in the modulation of the abnormal proteins functioning is strongly anticipated. From the fundamental research, all reviews in this issue are intrinsically aimed at clinical applications in the patients.

Following the first three basic research reviews on neuroendocrine tumorigenesis, the specific gene abnormality of signal transduction is discussed in the two subsequent articles focusing on an inactivating mutation in the *PRKA1A* gene encoding protein kinase A type 1A regulatory subunit in Carney Complex and primary pigmented nodular adrenocortical disease. The different clinical manifestation and the major role of cAMP pathway dysregulation in the two diseases are important to be elucidated, but even such rare neuroendcrine tumors can give insights into genotype-phenotype relationship as well as into clinical approaches to the appropriate management of patients.

As one of the ectopic hormone producing neoplasms, neuroendocrine tumors secreting GHRH are then reviewed from the standpoint of pathophysiology and clinical aspects. Although GHRH is infrequently implicated in the pathogenesis of acromegaly due to hypothalamic or ectopic hypersecretion, reasonable strategy for early and accurate diagnosis is essential and clinically needed. Besides the basic and clinical investigations, more practically oriented genetic counseling is another important topic that clinicians should

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be aware of, particularly of its psychological impact and ethical complexities in familiar and hereditary neuroendocrine tumors. Pursuing medical ethics issues, a well-balanced review follows that answers questions commonly arising in genetic counseling. Recent advancement of tumor imaging diagnosis for neuroendocrine tumors is also one of the topics here. Various applications of molecular targeting radiopharmaceuticals such as FDP and somatostatin receptor imaging using positron emission tomography are currently available. Two review articles discuss the benefits and limitations of diagnosis by tumor imaging for a wide variety of neuroendocrine tumors. Precise and more specific molecular targeting approaches to functional imaging can be expected to overcome constraints in the near future, including implementation of molecular imaging applications for tumors at different stages. Lastly, the treatment of various neuroendocrine tumors with somatostatin analogue is summarized. The characterization of tumor-specific receptors and appropriate use of somatostatin analogue can relieve symptoms and reduce hormone levels in patients with functioning neuroendocrine tumors but reduction in tumor size is unstable and rather unusual. It is also expected that the new types of analogues may be more beneficial for treatment.

The markers of final diagnosis of neuroendocrine tumors are generally accepted to be chromogranins by immunohistochemical staining together with or without visualization of specific hormones. Neuroendocrine cells are scattered all over the body from the skin to various internal organs. Further analysis of the relationship between the identified genotype and phenotype on histology and clinical course is essentially needed. This could be done through the establishment of a wide-ranged global research network of neuroendocrine tumors using the Chernobyl Tissue Bank [2] as a referring model of a combination of a collection of biological materials with a comprehensive database. Although the specific types of tumors such as carcinoids and non-carcinoid gastroenteropancreatic neuroendocrine tumors need to be further analyzed separately, all ten topics in this special issue of *Pituitary* are timely presented to grasp the current progress in the area and also to make a link between the knowledge and technology from bench (etiology, tumor metabolism, molecular genetics and pathophysiology) to bedside (medical ethics, diagnosis and treatment).

Finally, the great contribution of the invited authors is highly appreciated.

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